REMARKS

Upon entry of the foregoing amendments to the specification, the title has been amended. Also, the specification has been amended as shown above to remove URLs from the specification. No new matter has been added by the amendments to the title or the specification.

Applicants have cancelled Claim 27 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have added new Claims 28-30, which are supported by the original claims as filed. Also, Applicants have amended Claim 22 to remove reference to the Figure and to recite that the claimed antibody specifically binds to the polypeptide of SEQ ID NO: 57. Claim 22 has also been amended to recite an "isolated" antibody. Support for this amendment can be found in the specification at page 83, lines 2-11. Claim 25 has been amended into independent form. Claims 22-26 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed March 17, 2005. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Information Disclosure Statement

The Examiner states that the previously-filed information disclosure statements have been considered, but do not give sufficient identifying information to determine if the sequences constitute prior art.

Applicants submit herewith an Information Disclosure Statement that includes more detailed information regarding the BLAST results, including the publication date of the relevant sequences.

Specification

The Examiner states that a new title is required that is more clearly indicative of the invention to which the claims are directed. The title has been amended to recite "ANTIBODIES TO POLYPEPTIDES THAT INDUCE CELL PROLIFERATION."

Also, the Examiner states that the specification should be reviewed for the recitation of improper hyperlinks, and that all such recitations should be deleted or amended. Applicants have amended the specification to address the Examiner's concern. In particular, Applicants have replaced the hyperlinks with text that describes the location of the websites. The amended text no longer constitutes browser executable code.

Rejection under 35 U.S.C. §101 - Utility

The Examiner rejects Claims 22-27 under 35 U.S.C. §101 as lacking utility because allegedly the claims are not supported by a specific and substantial asserted utility, or a well established utility. The Examiner argues that the claimed invention is incomplete. The Examiner indicates that the specification asserts two specific utilities based upon positive results in two assays for the PRO4380 polypeptides to which the antibodies bind. However, the Examiner argues that neither utility is substantial.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." (1) A utility is "specific" when it is particular to the subject matter claimed. (2) With regard to substantial utility, "[a]ny reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01). (3) "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the Applicant's assertions." (M.P.E.P. 2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Here, the polypeptides to which the claimed antibodies bind have at least one asserted utility that is specific, substantial, and credible. For example, the claims have utility based upon Example 41 on page 168, which describes a mesangial cell proliferation assay. Example 41 shows that certain polypeptides act to induce proliferation of mesangial cells, and therefore, are useful for the treatment of various kidney disorders, for example, those associated with decreased mesangial cell functions, such as, Berger disease or other nephropathies associated with Schönlein-Henoch purpura, celiac disease, dermatitis herpetiformis or Crohn disease. As mentioned in Example 41, PRO4380 is one of polypeptides that tested positive in the assay.

The ability to induce mesangial cell proliferation is specific or particular to the PRO4380 polypeptides, and is not an ability common to all peptides generally. Also, the utility is substantial as treatment of the above-mentioned disorders provides a public benefit. Finally, one of ordinary skill in the art would recognize that the scientific assay results of Example 41 support

the credibility of the utility assertion. Thus, the PRO4380 polypeptides and the antibodies that bind to them have utility.

Nevertheless, the Examiner argues that Example 41 (Assay #92; page 168) fails to provide a substantial utility for the PRO4380 polypeptides and the claimed subject matter. In support, the Examiner relies upon an article by Rovin et al. (*Kidney Int'l*, 61:1293-1302, 2002). The Examiner reasons that Rovin et al. performed an assay that is similar to the assay of Example 41, and that according to Rovin et al. a 21% increase in proliferation above control is not statistically significant. Based upon that, the Examiner argues that a 15% increase in proliferation, as shown in Applicants' Example 41, must not be statistically significant. Therefore, the Examiner concludes that "Rovin et al. indicate that PRO4380 is not useful in the proliferation of kidney mesangial cells."

Respectfully, the article by Rovin et al. has been misunderstood or misinterpreted by the Examiner, and does not rebut the utility of the claims based upon Example 41. The passage from Rovin et al. does not indicate that 21% greater proliferation is not scientifically useful, important or significant, but instead indicates that that individual data point (21%) is statistically unreliable due to statistical errors.

The passage from Rovin et al. relied upon by the Examiner states:

> There was a small increase in proliferation index (21%) in response to 5 μmol/L ciglitazone, but this *did not reach significance*. (emphasis added).

This passage does not indicate that proliferation of 21% is not significant in terms of utility or scientific significance. Rather, the passage refers to whether the particular data point is statistically reliable or significant in terms of statistical error. In other words, "significance" as used in the cited passage refers to whether there is an overlap or non-overlap of standard deviations or errors in the data set. If there is an overlap between the control data point and the 5 μmol/L data point, then it is possible that there is no difference in proliferation between the control and the compound at 5 μmol/L, thus, that data point cannot be said to be reliable or significant. In the case of the data set showing a 21% increase, those data in fact are not statistically significant because the statistical error in their measurement overlaps with the statistical error of the control set. This is supported by reference to Figure 2A. As seen in Figure 2A, the error bars of the data point at 5 μmol/L overlap with the error bar range of the adjacent data point. Therefore, the 5 μmol/L data point was not statistically reliable or significant because

of the amount of statistical error associated with the data point. This does not mean that an increase of proliferation of 21% is not scientifically useful, important or significant, but means that Rovin's particular measurement of 21% may be incorrect or uncertain due to the amount of error for that data point. The fact that a single data point reported by Rovin et al. had excessive statistical error such that it "did not reach significance," does not mean that any other data point, including Applicants' data, are statistically insignificant, much less lacking in scientific utility.

Interestingly, the two sentences immediately following the passage relied upon by Examiner do not support the Examiner's reasoning:

> Similar results were found when troglitazone was used (Fig. 2B). Cell death occurred at concentrations greater than 15 μmol/L, and there was as small, but *significant* increase in proliferation index (18%) using 10 μmol/L troglitazone. (emphasis added).

Applicants assert that the term "significant" as used in Rovin et al. refers to whether the data are statistically reliable in terms of standard deviations or errors associated with the data point. This is demonstrated by Figure 2B which shows that at 10 μmol/L there was no error bar overlap with the control data point. Thus, that particular μmol/L data point was statistic reliable or "significant."

Therefore, Rovin et al. does not contradict the utility of the claims based upon Example 41. Further, Rovin et al. provides no reasons that would lead one skilled in the art to question the objective truth of the statement of utility. As demonstrated by Example 41, PRO4380 induced a significant increase in cell proliferation. Thus, Applicants assert that person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true based upon the results of Example 41. For the reasons discussed above, the claimed subject matter has a specific, substantial and credible utility.

Therefore, Applicants respectfully request reconsideration and withdrawal of the instant rejection under 35 U.S.C. § 101.

Rejections under 35 U.S.C. §112, first paragraph – Enablement

The Examiner rejected Claims 22-27 under 35 U.S.C. § 112, first paragraph. According to the Examiner, because the claimed invention is not supported by either a substantial asserted utility or a well established utility, one of skill in the art would not know how to use the invention.

Applicants submit that in the above discussion of the rejection under 35 U.S.C. § 101, Applicants have established a substantial, specific, and credible utility for the claimed antibodies and the polypeptides to which the antibodies bind. Specifically, the PRO4380 polypeptides, to which the claimed antibodies bind, have utility in inducing mesangial cell proliferation. Therefore, the claimed antibodies have utility.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 22-27 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner argues that the claims are indefinite due to the recitation in Claim 27 of "specifically binds." According to the Examiner, it is not clear what the difference is between an antibody that binds and an antibody that specifically binds. Claim 27 has been cancelled and Claim 22 amended to recite "specifically binds."

Also, the Examiner rejected Claim 25 as indefinite arguing that an antibody cannot be a fragment of itself. As set forth above, Claim 25 has been amended into independent form.

In view of the amendments, Applicants respectfully request reconsideration and withdrawal of the instant rejections under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. §102 – Anticipation

The Examiner rejects Claims 22-25 and 27 as anticipated under 35 U.S.C. § 102(a) by Ruben et al. (WO 99/58660) (hereinafter Ruben), which was published on November 18, 1999. The Examiner states that Ruben teaches an amino acid sequence (SEQ ID NO: 131) that is 99.6% identical to SEQ ID NO: 57 of the instant application. The Examiner asserts that Ruben teaches "specific preferred epitopes along the entire length of the protein which can be used for the production of antibodies." Therefore, the Examiner argues that Ruben anticipates the claims. Applicants respectfully traverse.

Attached herewith is the Declaration of Audrey Goddard, Paul J. Godowski, Austin L. Gurney, James Pan, Colin K. Watanabe and William I. Wood under 37 C.F.R. §1.131 (referred to hereafter as "the Declaration of Goddard et al."), which establishes that the presently claimed invention antedates the publication date of Ruben. The Declaration of Goddard et al. establishes that the presently claimed subject matter was conceived of and reduced to practice prior to the publication date of Ruben, November 18, 1999. Thus, Applicants respectfully submit that the

cited reference is not available as prior art, and request that the rejections under 35 USC §102(a) be withdrawn.

As set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." *See also*, M.P.E.P. § 715. "The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... at least conception being at a date prior to the effective date of the reference." *See* M.P.E.P. § 715.07 (emphasis in original). The showing of facts must be sufficient to show "conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice." *See id.*

Ruben was published on November 18, 1999. Ruben is cited as a 102(a) reference because it allegedly discloses antibodies to an amino acid sequence that is 99.6% identical to the sequence of SEQ ID NO: 57. However, as set forth below, Applicants were in possession of SEQ ID NO: 57, and antibodies to the same, prior to the publication date of Ruben.

The Declaration and attached Exhibit A demonstrate that the polypeptide sequence of SEQ ID NO:57, to which the claimed antibodies and antibody fragments bind, was conceived by Applicants prior to November 18, 1999. Furthermore, as evidenced by the Declaration and Exhibit B, Applicants reduced the polypeptide to practice prior to the publication date of Ruben, by performing assays to confirm the function of the polypeptide to which the antibodies bind. Also, Applicants worked with Genentech, Inc. to diligently prepare and file U.S. Provisional Application No. 60/130,359 and non-provisional application PCT/US00/05601, which teach how to make and use the claimed antibodies and fragments. Therefore, Applicants possessed the claimed subject matter prior to the publication date of Ruben et al.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102.

Rejection under 35 U.S.C. §103 – Obviousness

The Examiner rejects Claim 26 under 35 U.S.C. § 103(a) as being upatentable over Ruben (WO 99/58660), in view of Holmes et al. (Current Protocols in Immunology, pp. 5.35 –

5.38, 1995). The Examiner acknowledges that Ruben does not disclose labeled antibody, but argues that Holmes teaches the conjugation of various labels to antibodies.

As discussed above in connection with the anticipation rejection under § 102(a), Ruben does not anticipate because Applicants possessed the claimed subject matter prior to the publication date of Ruben. Similarly, Claim 26 cannot be obvious over Ruben. Holmes does not teach antibodies that bind to SEQ ID NO:57, and therefore does not anticipate or obviate Claim 26 in the absence of Ruben.

Therefore, Applicants request reconsideration and withdrawal of the instant rejection under § 103(a).

Conclusion

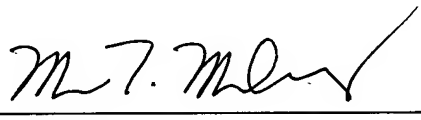
The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 16, 2005

By: 

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DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Luc Desnoyers, Dan L. Eaton, Timothy L. Stewart and Zemin Zhang.